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Efficacy and tolerability of levetiracetam during 1-year follow-up in patients with refractory epilepsy

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Problem: Levetiracetam (LEV) is a new antiepileptic drug shown to be effective for the treatment of partial seizures in pivotal clinical trials. We investigated the long-term efficacy and tolerability of LEV as add-on therapy, regardless of seizure type, especially in persons who would not be eligible for clinical trials due to factors such as mental retardation and concomitant psychiatric disorders.
Methods: Ninety-eight patients participated and were followed for 1 year. Demographic data, seizure frequency, and side effects were recorded at baseline and during the 1-year follow-up. The first 35 patients were given LEV at a starting dose of 500 mg b.i.d. with weekly increments of 1000 mg (fast titration). The other patients were given LEV with a starting dose of 250 mg b.i.d. with weekly increments of 250 mg (slow titration).
Results: Fourteen patients were completely seizure free after titration to effective dose and 57 were responders with >50% seizure reduction for the first year. In the group with generalized seizures, 1 out of 19 became seizure free, but 8 patients had >50% decrease. Average dose at 1 year was 1900 mg (±900). Seventeen of 38 discontinuations were due to adverse effects and 21 were due to lack of efficacy. With fast titration, 15 out of 35 (43%) experienced tiredness during the first 12 weeks, and with slower titration 20 of 63 (32%) experienced tiredness. The difference was not statistically significant.

Four out of the five patients who discontinued due to behavioral adverse events (mainly irritability) previously had behavioral problems and/or mental retardation. One patient discontinued due to psychosis.
Conclusions: Levetiracetam appears to be well tolerated in patients with severe epilepsy and shows efficacy in a long-term follow-up. Behavioral adverse events were noted in a small number of patients and occurred mainly in patients who had a history of behavioral disturbance or were mentally retarded. These data from an open population are consistent with the findings of clinical trials.

Key words: antiepileptic drugs; levetiracetam; prospective trial; efficacy; tolerability.

INTRODUCTION

Levetiracetam (LEV) is a new antiepileptic drug (AED) recently approved for use in the USA and EU countries. It has been available since April 2000 in the USA and available for compassionate use in Sweden since August 2000 and as a commercial drug since January 2001. Registration was based on clinical trials and safety data from 1422 patients with epilepsy. A total of 3000 people have been treated with LEV before registration.

So far there have been no published postmarketing prospective reports concerning the long-term clinical efficacy or safety of LEV in a clinical setting. This, therefore, is, to our knowledge, the first report of the results of long-term treatment of consecutive patients with LEV who suffer from various types of seizures and syndromes.

METHODS

Design

This is a single-center, prospective add-on open-label treatment study.

Patient eligibility criteria were maintenance of a seizure diary by the patient or a caretaker for the 3 months before enrollment, and continued seizures that were refractory to all previous treatments. There was no restriction to specific seizure type or epilepsy syndrome. Ninety-eight patients were enrolled in the study to receive LEV as adjunctive therapy.

Patients were stratified into those with epilepsy of focal origin, those with generalized symptomatic epilepsy (as Lennox–Gastaut Syndrome), and those with generalized idiopathic epilepsies (absence epilepsy, juvenile myoclonic epilepsy, and included in this group was two patients, one with Baltic myoclonic epilepsy (BME) and one with Lafora body disease (LBD)).

LEV dose

The first 35 patients were given LEV according to labeling at a starting dose of 500 mg twice daily and increased with weekly increments of 1000 to 1000 mg twice daily. If efficacy was not satisfactory, the dose was then increased to 1500 mg twice daily. The rest of the patients, from patient 36 to 98, began with a starting dose of 250 mg day^{-1} and increased by 250 mg every week to 500 mg twice daily. If seizure control was not satisfactory and there were no side effects, then the dose was increased by 500 mg weekly to 2000 mg day^{-1} and then if necessary to 3000 mg day^{-1}.

Follow-up

Patients came for a clinic visit approximately every third month for 1 year. Seizure frequency and side effects were recorded using patient diaries. The 3-month baseline seizure frequency was determined by reviewing the preexisting patient diaries. Changes in concomitant medication were done only if a patient reported side effects of concomitant AEDs before starting LEV (such as peripheral field deficits due to vigabatrin or weight gain due to valproate). No new therapies were added during the entire follow-up period.

Efficacy variables

Efficacy was measured as seizure freedom, 75–99% seizure reduction, 50–74% seizure reduction, 25–49% seizure reduction, no response up to 25% seizure reduction, and increased seizures. The number of patients who became seizure free after dose titration was recorded. To evaluate a possible tolerance effect, patients who achieved a 90–100% seizure reduction and then experienced a loss of the original efficacy were registered.

Side effects

Side effects were recorded and divided into side effects causing withdrawal, those occurring during the first 12 weeks of therapy and those occurring or continuing later than 12 weeks after treatment started.

Statistical analysis

Parametric data are expressed as mean and standard deviation or range. Nonparametric data are expressed as median and range. Proportions are expressed as percentages. The Kruskal–Wallis test was used for multiple comparisons in efficacy between seizure types. Correlations were tested with Spearman's rank correlation, while comparisons in adverse events were tested with Chi-square. No corrections for multiple comparisons were made. A Kaplan–Meier survival curve was also generated using the Statview software.

RESULTS

Patient characteristics

A total of 98 patients participated in the study. Seventy-nine had focal-onset epilepsy, 12 had symptomatic generalized epilepsy, 4 had generalized idiopathic epilepsy with absences and generalized tonic–clonic seizures, 1 had LBD, 1 had BME, and 1 had juvenile myoclonic epilepsy. The average age was 38.9 (range:12–68 years) and the average life-span with epilepsy was 69% ($\pm$0.25%). The average baseline seizure frequency was 14 seizures per month but the range varied from 1 to 110 seizures per month, (SD = 21.5). Fifty-one of the 98 patients were males. Ten patients previously had serious psychiatric disturbances, 22 were mentally handicapped, and 33 patients received active vagus nerve stimulation (VNS), although a total of 44 had tried VNS. Sixteen had previously undergone resective epilepsy surgery. In other words, most of the patients in this study were refractory to other conventional treatments. Twenty-four patients were taking one other concomitant AED, 45 were taking two, 22 were taking three, 5 were taking four other AEDs and 1 took five concomitant AEDs. The AEDs that were taken by 10 or more patients were: carbamazepine (n = 52), topiramate (25), valproic acid (22), phenytoin (20), lamotrigin (19), vigabatrin (17), clobazam (16), and phenobarbital (10). One patient received LEV as monotherapy from the start of the study as she had stopped the other AEDs because of lack of efficacy.

Efficacy

Patients with focal-onset epilepsy

Seventy-nine patients were included in the partial-onset seizure group. All but three had two or more seizures

Table 1: Reduction in seizure frequency.

Epilepsy type	Localized	Generalized idiopathic	Generalized symptomatic
Total	$n = 79$	$n = 7$	$n = 12$
Seizure free	13 (16%)	1 (14%)	0 (0%)
75–99% reduction	26 (33%)	2 (29%)	2 (17%)
50–74% reduction	10 (13%)	2 (29%)	1 (8%)
25–49% reduction	1 (1%)	0 (0%)	1 (8%)
0–24% reduction	27 (34%)	2 (29%)	7 (68%)
Increased seizures	2 (3%)	0 (0%)	1 (8%)

The number and percentage of the patients with different types of epilepsy syndromes divided according to the change in seizure frequency compared to baseline observed over a 6-month period after the introduction of LEV.

per month (median: 5 per month). Seizures types consisted of simple partial, complex partial, and/or secondarily generalized seizures. During the year of treatment, a total of 49 patients had a >50% seizure reduction, 27 (34%) did not experience any significant seizure reduction, and 2 (3%) actually reported an increase in seizures (see Table 1). One (1%) patient experienced a 25–50% seizure reduction, 10 (13%) had a 50–74% seizure reduction, 26 (33%) had a 75–99% reduction in seizures, and 13 (16%) were seizure free after titration to effective dose. The average dose for the patients that continued to take LEV throughout the study was 1900 mg day^{-1} (range: 250–4000 mg day^{-1}). For the patients who were seizure free, the average dose was 1500 mg day^{-1} (range: 1000–3000). Fifteen patients were seizure free from the start of therapy but four patients (not included in the final seizure-free group count) had a relapse after 1–3 months. Only one of these four patients had previously reduced their concomitant AED. Twenty-eight withdrew from therapy with LEV after a median of 23 weeks (range 2–59).

Patients with symptomatic generalized epilepsy

Twelve patients suffered from symptomatic generalized epilepsy. In this group, one patient experienced an increase in seizures, seven had no response, and three were responders with >75% seizure reduction (Table 1). Seven stopped LEV after an average of 2 months of treatment.

Patients with idiopathic generalized seizures

This group was comprised of seven patients. Four had refractory absence seizures with generalized tonic–clonic seizures. One patient had BME. One had juvenile myoclonic epilepsy and one had LBD. The patient with juvenile myoclonic epilepsy and one with absence epilepsy did not respond at all to LEV. The patients with BME and LBD experienced a >50% reduction in seizure frequency and myoclonic jerks. One patient with absence epilepsy had a 30% decrease in seizures, one had a 90% seizure reduction, and one was seizure free for 1 year on a dose of 1000 mg day^{-1}.

Correlations between efficacy and other variables

Using the Kruskal–Wallis test, no significant differences were found between seizures types (simple partial, complex partial, secondary generalized seizures, absences, myoclonia, primary generalized seizures or atonic seizures) and efficacy ($P = 0.179$). Using the Spearman's rank correlation, there were no significant correlation between the number of AEDs taken before adding LEV and efficacy ($r = 0.2$; $P = 0.12$), or the duration of epilepsy (percent of life with epilepsy) and response to treatment ($r = 0.2$; $P = 0.1$). Patients with VNS responded in the same way as those without ($P = 0.2$).

Of the 14 patients who became seizure free, no one had more than 11 seizures per month before adding LEV. By the end of the first year, 61% ($n = 60$) were still taking LEV while 39% ($n = 38$) had dropped out (see Fig. 1).

Adverse events

Forty-two patients reported having side effects while taking LEV. Tiredness was the primary side effect reported. Of the 35 patients started on fast titration of LEV (500 mg b.i.d. for the first week and 1000 b.i.d. for the second week), 15 patients complained of initial tiredness. This did not resolve in three after more than 12 weeks of treatment. In the 63 patients with slow titration (250 mg day^{-1} for the first week with an increase of 250 mg week^{-1} up to 2000 mg day^{-1}), 20 complained of tiredness initially and 10 out of the 59 still treated still had symptoms after 12 weeks of treatment. The frequency of tiredness, any other adverse event, or discontinuation of LEV, did not differ significantly between the groups. Other side effects were irritation ($n = 5$ initially and 7 after 12 weeks). Other side effects were pruritis ($n = 3$), increased seizures ($n = 3$), and psychosis ($n = 1$). Nineteen patients stopped treatment due to side effects without or in combination with the lack of effect. Another 17

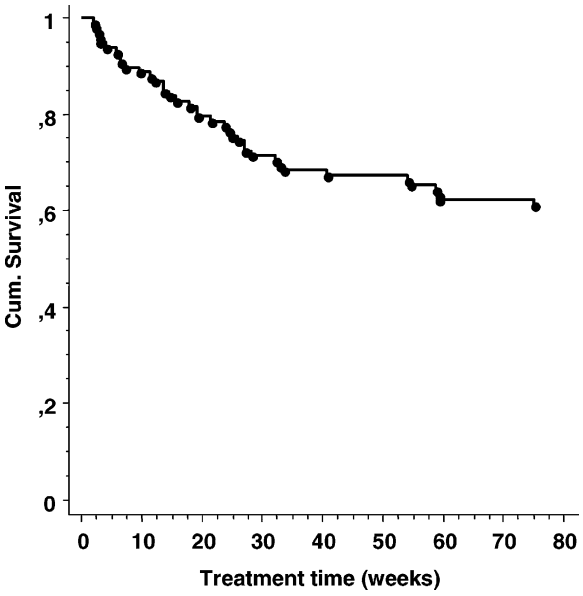

Fig. 1: Kaplan–Meier survival curve for 1-year treatment with LEV showing the percent of patients still being treated.

patients stopped treatment solely due to lack of effect. In total, 38 patients discontinued LEV (see Table 2). No deaths occurred in this cohort of patients. There have been no pregnancies reported so far.

Behavioral adverse events, mainly irritability, were reported by five during the first 12 weeks of treatment and by seven after the first 12 weeks of treatment. This led to discontinuation of the drug in four of these patients. Three stopped by 12 weeks and one stopped only later on. The type of irritation in the four patients who discontinued could rather be called aggression. When the drug was stopped aggression and irritation resolved immediately. All but one of the patients who exhibited aggression and who were subsequently discontinued previously had behavioral problems and mental retardation. One patient discontinued the drug due to psychosis. He, previously had behavioral disturbances with bouts of psychosis, was mentally retarded and his epilepsy was very refractory. He did not experience any seizure reduction with LEV.

DISCUSSION

Refractory epilepsy is a difficult condition to treat and most patients, regardless of syndrome, usually try numerous drugs and interventions in an attempt to reduce seizure frequency and ultimately become seizure free. The patients in this study all had intractable epilepsy and were interested in trying LEV when it became available, as very few would have met all inclusion criteria for participation in a clinical trial, due to factors such as mental retardation, number of concomitant AEDs, and previous psychiatric illness. Thus, it is encouraging to find that efficacy was very good in 45% (>75% seizure reduction) in this difficult to treat group of patients. This compares very favorable with the efficacy profiles of other new AEDs[1].

Long-term follow-up from the clinical trials of LEV, mainly concerning patients with focal-onset seizures support the results of our study. Retention rates were 60% after 1 year and 32% after 5 years[2]. The responder rate for >50% seizure reduction in their study was 39%. There were 13% who were seizure free for the last 6 months of treatment and 8% who were seizure free at the last year.

The side effect profile of LEV seems to be, at least in our study, limited to fatigue or tiredness, and some reports of irritation and aggression. The tiredness described by our patients was primarily one of lack of energy, but not necessarily sleepiness. Slower titration than is recommended in the registration instructions did not significantly lower the complaint rate. Still our impression is that slow titration will enable the physician and patient to evaluate the effect and side effects of the drug in a more controlled setting. From the pooled data from the randomized control trials (RCT), somnolence was the most frequent reported side effect with 14% of patients complaining and 12% complaining about asthenia[3]. In our study, the two side effects were grouped into the single term of tiredness because it was not possible to always differentiate between the two problems as they were often intertwined. Irritation was also an initial complaint, but only in five patients and in five after 12

Table 2: Number of patients who experienced adverse events after the introduction of LEV.

Side effect	Early (<12 weeks), $n = 98$	Late (>12 weeks), $n = 88$	Reason for withdrawal, $n = 98$
Irritated	5 (5%)	7 (8%)	4 (4%)
Tiredness	36 (37%)	13 (15%)	10 (10%)
Rash and itch	0 (0%)	3 (3%)	1 (1%)
Gastrointestinal disturbance	0 (0%)	0 (0%)	0 (0%)
Psychosis	0 (0%)	1 (1%)	1 (1%)
Paresis	1 (1%)	0 (0%)	1 (1%)
Increased seizures	2 (2%)	1 (1%)	3 (3%)

Data is presented as number (percentage).

weeks, of which three developed this side effect after 12 weeks of therapy. Concerning the side effect of irritation, usually it was a relative who reported that the patient could become more easily angry or stressed. In the pooled placebo-controlled trial data[3], irritation was not reported as a major adverse event. Perhaps this discrepancy occurred because our patients were not people who could be included in a clinical trial because they often had behavioral and psychiatric disorders as well as mental handicaps. Interestingly, the behavioral adverse events were not related to seizure reduction so 'forced normalization' did not seem to be an important factor in this study.

The shortcomings of this study are that (1) it is a single center study, but at least all the patients could be meticulously accounted for; (2) it is not a randomized placebo-controlled study but it is very hard to follow refractory patients in a blinded fashion for long-term trials and is probably not ethical to treat with placebo for such extended periods of time.

In the placebo-controlled studies and long-term follow-up studies[2–6], doses were predetermined by protocol and most patients remained on the dose designated by the study if it was tolerable. In our study, we could titrate slowly to response, and, therefore, found that many of our patients achieved good efficacy at lower doses than expected. In fact, the patients who became seizure free often did so on lower doses than those who did not (average dose 1500 mg compared to average dose 1900 mg for nonseizure-free patients). The interesting feature of this drug was that most of the seizure-free patients became seizure free early on during titration, even from the very first tablet. Most often this result was sustained but four of the patients spontaneously developed seizures again after 1–4 months. This is often observed when adding on AED therapies, but there did not seem to be evidence of tolerance in the majority of patients in this study. Once a level of efficacy was achieved, it seemed to be sustained in most patients over the entire study period as evidenced by the survival rates.

All patients, regardless of seizure type, were included in this investigation. Although most were patients with focal-onset epilepsy with simple partial, complex partial, and secondarily generalized seizure types, 19 of 98 patients had either generalized symptomatic or generalized idiopathic epilepsy syndromes. In the generalized symptomatic group, only three were truly responders. The others had either marginal effects or none at all. Seizure types in this group were atonic seizures, generalized tonic or tonic–clonic seizures or atypical absences. The patients in this group had previously tried multiple therapies before so it is impossible to determine if LEV would be effective in symptomatic generalized epilepsy judging by the result of this small sample. The few patients in the idiopathic generalized epilepsy group tended to do better. Patient with unusual seizure types as seen in BME and LBD were included and both responded very favorably with reduction of seizures and stimulus sensitive myoclonia. Piracetam, which has similar characteristics to LEV and was developed from the same parent compound, is a highly effective drug for myoclonia. Perhaps LEV and piracetam share the same mechanistic properties in controlling myoclonus. The full mechanism of action of LEV is, however, so far undisclosed.

In *conclusion*, LEV seems to be a broad spectrum AED with surprisingly few side effects. Its efficacy in focal-onset seizures is impressive. Efficacy with this drug in other epilepsy syndromes remains promising, but new ongoing placebo-controlled studies will further clarify its efficacy. Tolerability seems to be good in all patients no matter seizure type or epilepsy syndrome.

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